REMARKS

The Office Action indicates that the specification should be amended to reflect the priority claim; such an amendment has been made above.

Rejections Under 35 U.S.C. §112, second paragraph

Claims 13 and 20 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and claim the subject matter of the invention. This rejection is respectfully traversed.

More specifically, Claims 13 and 20 were deemed vague and indefinite in the use of the term "products of co-culture"; the Office Action states that the definition provided for such products encompasses "virtually any matter including any product of the cellular metabolism of tumor and dendritic cells. This is unacceptably indefinite." Applicants defined "co-culture" in the specification to refer to a culture of cells in which there is a population of at least two different cell types. "Products of" this co-culture refers to the matter resulting from the co-culture of the two cell types and includes, for example, cells that have become fused together, cells that have not become fused together, and cellular components including but not limited to the cytoplasm and nuclear matter released from the cell upon cell death or rupture by other processes. One skilled in the art would understand from this disclosure that during co-culture a stimulator complex which contains tumor antigen and molecules necessary for antigen presentation to T-cells is formed; the stimulator complex formed would include, for example, fused cells, unfused dendritic cells which have internalized or become associated with antigenic cellular components, apoptotic bodies, debris from necrotic cells or released cytosolic antigens, and unfused tumor cells which have internalized or become associated with dendritic cell components relative to antigen presentation function. It is clear from the specification, therefore, what Applicants intend by the term "products of co-culture". Moreover, the specification indicates that any means of co-culturing cells known in the art can be used. A preferred method of co-culturing is also provided, in which the two cell types are combined, centrifuged to form a pellet, and the pellet incubated. Thus, not only have Applicants defined what they have meant

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by the term "products of co-culture" but have clearly taught one skilled in the art how to prepare such products. As such, it is respectfully submitted that one skilled in the art could practice the claimed invention based upon the disclosure without undue experimentation. Therefore, the metes and bounds of the terms used in Claims 13 and 20 are not indefinite.

Rejections under 35 U.S.C. §103(a)

Claims 13-14 and 17-24 were rejected under 35 U.S.C. §103 as allegedly being unpatentable over *Guo, et al.* in view of either *Murphy, et al.* (U.S. Patent No. 5,788,963) or *Steinman, et al.* (U.S. Patent No. 5,851,756). This rejection is respectfully traversed.

Guo is cited as allegedly teaching "co-culture of APC with tumor cells with fusion of APC with tumor as a way of surmounting antigen processing problems . . . ." The Office Action likens the fusion product taught by *Guo* to the products of co-culture of the present invention. There are several significant distinctions between these two products, however. *Guo* does not teach co-culture of the cells and the use of the products which result from the co-culture. Rather, *Guo* is directed solely to the fusion of tumor cells, specifically with activated B cells. The fusion product of two cell types is distinct from the products of co-culture of the two cell types. This is evident from the present case, in which claims directed to fusion products and claims directed to products of co-culture were subject to a restriction requirement. Although Applicants' definition of "products of co-culture" includes those cells that may have become fused, the term encompasses numerous products of cell metabolism and not fusion products alone. Indeed, since no fusion promoter (such as PEG) is used to co-culture two cell types, the percentage of "fused" cells in the products of co-culture would be relatively small. In any event, it is clear that *Guo* does not encompass co-culture products claimed by Applicants. As discussed in *Guo* on page 520, column 1, first full paragraph, mixtures of tumor cells with activated B cells were not effective in inducing protective immunity. There is no teaching or suggestion by *Guo* that mixing or co-culturing the cells would be sufficient to induce protective immunity; indeed, the

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suggestion is the opposite. Moreover, *Guo* teaches that after fusion, a stable tumor cell-B cell fusion product must be selected; the present invention eliminates the need for the selection step. Thus, it is submitted that *Guo* does not teach formulations comprising products of co-cultures as recited in the pending claims.

In addition to failing to teach products of co-culture, *Guo* also fails to teach use of the elected species of antigen presenting cells (APCs), namely dendritic cells; this is conceded in the Office Action. More specifically, *Guo* is limited only to activated B cells. As noted in the specification (page 2, lines 29-30), use of dendritic cells as taught in the present invention provides an advantage not taught by *Guo*, in that activation of dendritic cells is not required whereas activation of B cells is.

To overcome the shortcomings in the primary reference, the Office Action further cites to either *Steinman* or *Murphy*. *Steinman* is cited as allegedly teaching a method of *in vitro* proliferation of dendritic cell precursors and their use to process antigens for induction of immune responses. *Murphy* is cited as allegedly teaching, among other things, the importance of dendritic cells as APCs and their superiority to other types of APCs. For a combination of references to be properly applied, there must be some teaching or suggestion in the references along the lines of the current invention. (See, for example, *In re Sernaker*, 217 USPQ1 (Fed. Cir. 1983), a copy of which is enclosed.) Applicants respectfully submit that the requisite motivation for combining the references is lacking here. Specifically, *Guo* teaches that activated B cells are the most effective antigen presenting cells. (See *Guo*, page 518, column 1, second paragraph). Even if *Murphy* does teach the superiority of dendritic cells over other antigen presenting cells, which Applicants do not concede, this is in direct contrast to the teachings of *Guo*. Thus, two sources teach two opposite conclusions. Furthermore, *Steinman* specifically teaches the removal of B cells from their dendritic cell precursor formulations, which suggests that B cells and dendritic cells are not compatible, let alone interchangeable. (See *Steinman*, column 11, line 58 through column 12, line 1.) It therefore cannot be said that the references motivate a combination such as that which would render the present invention obvious.

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In any event, Applicants respectfully submit that the methodologies taught by both *Steinman* and *Murphy* are so distinct from that taught by *Guo* that there would not be a reasonable expectation of success that substitution of dendritic cells for activated B cells would result in the formulations claimed by Applicants. *Steinman* fails to teach or suggest antigen loading of dendritic cells using whole tumor cells themselves as the source of antigen. It is simply not obvious from the teachings of *Steinman*, alone or in combination with *Guo*, that dendritic cells or any other type of cell can internalize or associate with whole cells in an immunogenic way.

Similarly, *Murphy* appears to teach only the exposure of dendritic cells to specific, defined prostate cancer antigens, or to lysates or fractionated lysates as potential sources for these antigens. There does not appear to be any teaching or suggestion in *Murphy* of the use of whole tumor cells as a source of antigen, or that dendritic cells can associate with antigens from whole tumor cells. *Murphy* appears only to teach the use of antigens in a soluble protein form. (See, *Murphy*, column 10, lines 47-51.) Neither *Steinman* nor *Murphy* provide the advantages of the present invention, namely eliminating the labor and time intensive step of processing tumor cells to make antigenic derivatives from whole cells.

It is therefore respectfully submitted that even if the references were properly combined, which Applicants do no concede, the combination would not result in the present invention. *Guo* simply does not teach the use of products of co-culture as recited by Applicants, so the substitution of dendritic cells for activated B cells does not yield the present invention. In addition, none of the references teach or suggest a co-culture utilizing dendritic cells, or any other type of antigen presenting cell, with tumor cells themselves. For all of the above reasons, it is respectfully submitted that Claims 13-14 and 17-24 are patentable over the combination of references.

Claims 13 and 15 were rejected under 35 U.S.C. §103 as allegedly being unpatentable over *Guo* in view of either *Murphy* or *Steinman* and further in view of *Zeid, et al.* This rejection is respectfully traversed.

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The comments made above regarding *Guo*, *Murphy* and *Steinman* apply equally here. The combination of references fails to teach formulations or pharmaceutical compositions comprising the products of co-culture of dendritic cells and any type of tumor cell. The additional citation to *Zeid* does not overcome this shortcoming.

Zeid is cited as allegedly teaching that patients whose lung carcinomas contained high densities of dendritic cells had a higher survival rate than patients who had few dendritic cells in their tumors. The article is further cited as allegedly teaching that death of tumor cells *in vivo* is associated with a high density of dendritic cells and lymphocytes; the Office Action cites the references as therefore allegedly "implying the effect of sensitized T lymphocytes acting specifically against the target tumor cells." Applicants respectfully disagree that this implication can be drawn. Although *Zeid* may have observed that high levels of dendritic cells in tumors resulted in a higher level of survival, there is no teaching or suggestion in the reference that the dendritic cells have been treated in the manner of the present claims. More specifically, Applicants' dendritic cells have been co-cultured with whole tumor cells, so that the dendritic cells present antigens found in those tumor cells. There is no teaching or suggestion in *Zeid* that the dendritic cells are acting in a similar manner. Nor is there any teaching or suggestion in *Zeid* of antigen transfer from tumor cells to dendritic cells or trafficking of dendritic cells from the tumor to the lymph node where T-cells would be activated. None of the reasons suggested by *Zeid* for their observed correlation renders obvious the present invention. In addition, the fact that *Zeid* observed this phenomenon in lung cells does not render obvious Applicants' use of lung carcinoma cells; *Zeid* does not appear to have investigated the dendritic cell population in any other kind of tumor, and therefore, the conclusion cannot be drawn that lung carcinoma cells would provide the dendritic cell/survival correlation whereas other cancer cells would not. Thus, the teachings of *Zeid* cannot be said to render obvious the present invention as it relates to the elected species of lung carcinoma cells. For all

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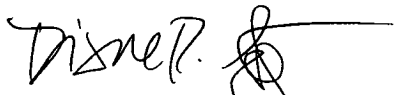
of these reasons, Applicants respectfully submit that the combination of references does not render Claims 13 and 15 obvious.

SUMMARY

Applicants respectfully submit that the above comments have addressed the rejection under 35 U.S.C. §112, second paragraph, in that the term "products of co-culture" would be both understood and could be practiced by one skilled in the art. In addition, Applicants respectfully submit that the combinations relied on under 35 U.S.C. §103 do not render obvious the presently claimed invention. For all of the above reasons, it is submitted that Claims 13 through 15 and 17 through 24 are patentable over the art of record and a Notice of Allowance is respectfully requested at an early date.

Respectfully submitted



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